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MMed (Neurosurgery) Research Report

Title:

The Underlying Causes and Management of Intracranial Subdural Empyema in the Neurosurgery Department, Chris Hani Baragwanath Academic Hospital

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Drs Karanja (UKZN) and Thobejane (UP) provided the inspiration to perform an empyema study at Chris Hani Baragwanath Academic Hospital. They challenged me to provide the answers to my own questions, as they had done for themselves at their respective institutions.

Abstract

Intracranial subdural empyema (SDE) is a potentially life-threatening condition. A retrospective study of the Chris Hani Baragwanath Academic Hospital's neurosurgery unit's SDE patients revealed a mean age of presentation of 15 years and male predominance (70%). In 61.7% SDE was linked with sinusitis and in 83% with immunocompetence. There was a statistically significant correlation between immunocompromise and death (40% mortality rate in the immunocompromised subset). Among the patients' culture positive specimen, 57.1% yielded a *Streptococcus spp.*, gram negative isolates were found in patients with immunocompromise or previous head trauma/surgery, and 78.6% of the micro-organisms were sensitive to 3rd generation cephalosporins. There was an 86.7% survival rate. A determinant of residual neurological deficit could not be found among the parameters investigated.

Keywords: intracranial subdural empyema, complicated sinusitis, burrholes

Introduction

Intracranial subdural empyema (SDE) was considered a complication of e.g. cranial/upper respiratory tract infection or previous cranial surgery/trauma. Despite advances in the management of respiratory tract infections and sterile operative technique, the problem still arose. The resounding message from first world researchers was that the occurrence of subdural empyema was rare.[1,4,5]

The referenced publications and the patients encountered at the Chris Hani Baragwanath Academic Hospital (CHBAH) neurosurgery unit led us to this hypothesis: subdural empyema was frequently a complication of sinusitis. The primary objectives were**:** to define SDE risk factors; to state the

demographics of SDE patients. The secondary objective was to quantify possible areas of improvement in the CHBAH neurosurgery unit's management of SDE patients.

Methods

The study design was a cross-sectional retrospective audit. The study population was: all patients who presented with subdural empyema to the neurosurgery department of CHBAH. The study period was from 01 January 2006 to 31 December 2015. The hand-written database of the CHBAH neurosurgery department was used to shortlist the patients admitted during the study period with the condition (intracranial SDE). The appropriate patients' files were then retrieved from the hospital's records.

The results were compared to relevant articles (and contributory, related articles cited by meta-analyses' authors) found by means of a Medline search for publications dated post-1990 using the keywords "intracranial subdural empyema".

The inclusion criteria were all patients referred to the neurosurgery department of CHBAH, admitted with post-contrast/-gadolinium CT/MRI scan evidence of SDE, and treated by a neurosurgeon with or without the involvement of another specialty. Exclusion criteria were admission by any department other than the neurosurgery unit of Chris Hani Baragwanath Academic Hospital, and patients (who met the clinical and radiological criteria) whose hospital records were lost.

The University of the Witwatersrand ethics committee granted permission for the study to run. The CHBAH neurosurgery head of department (database gatekeeper) consented to the use of the unit's

data. The Chief Executive Officer of CHBAH granted access to hospital records. Patient identifiers were not published.

The SDE management protocol (adjusted on a case by case basis as per the admitting consultant's opinion) was instituted for patients referred from another hospital/department with proven (on contrasted brain CT/MRI scan) subdural empyema. Those presenting with a Glasgow Coma Scale of 8 or less, or in status epilepticus were intubated and given ventilatory support according to each patient's needs. Empiric intravenous antibiotics (the default combination was penicillin, metronidazole and chloramphenicol; a third generation cephalosporin or vancomycin were used instead of penicillin at the discretion of the admitting consultant) and an anti-seizure agent (the default drug was phenytoin) were administered and haemodynamics stabilised (in unstable patients) while the patient awaited drainage of the collection on the emergency theatre list. The default mode of surgery was burrhole drainage. Craniotomies were generally reserved for patients with tenacious, recurrent collections. Conservative treatment was reserved for patients with small collections of 3cc or less, especially the loculated type.

The specimen sent for laboratory analysis included blood for admission full blood count (which included WCC, white cell count) and C-reactive protein (CRP), and pus (drained intra-operatively) for microscopy, culture and sensitivity. Antibiotics were then tailored to the sensitivity of the microbial isolate. Chemical thromboprophylaxis (in patients older than 13 years) and physiotherapy (with or without speech and/or occupational therapy) were supplied within 48 hours post-surgery. Intravenous antibiotics were administered for 2 weeks. The patients received oral antibiotics for an additional 4 weeks. Following the completion of the intravenous antibiotic course, patients were discharged once the serial 5-7 daily post-operative repeat scan showed adequate drainage (residual collection of 3cc or less).

Drainage surgery was revised when the result of a previous attempt was deemed insufficient on imaging. The rescan was done sooner if a patient deteriorated acutely. The CRP and WCC were also repeated during the admission period. Thus, the end points of the study were either death or both discharge from hospital as well as the following:

- completion of the intravenous antibiotic course;
- no significant suppurative intracranial collection on repeat post-contrast CT scan images;
- clinical resolution of toxic state (apyrexia and haemodynamic stability);
- normalisation or trend towards normalisation of septic markers.

Confounding variables were delays in diagnosis/referral of patients, that the patients' presenting severity of illness could have biased the choice of surgical extent, and mixed microorganism culture results.

The variables (age, gender, presenting symptoms, eye involvement, presence of immunocompromise, history and timing of sinusitis/otitis media/dental extraction/head trauma/ neurosurgery, antibiotics administered, nature of surgical intervention, microorganism isolate, sensitivity of microorganism isolate, presence of residual neurological deficit, duration of hospital stay and mortality) were classified according to scale (continuous vs categorical/ordinal). STATISTICA® 12 software was used to analyse the raw data from an Excel® spreadsheet. Values unavailable from the patient records were excluded from the calculations. Continuous variables' N, mean, median, interquartile range and 95% confidence intervals, and categorical variables' N and percentages were calculated. Continuous variables were tested for correlation to categorical variables (plotted on histograms and subjected to Leven's Test). If available data (N) was > 30 and normal, parametric testing was done. Otherwise, the Mann Whitney U-Test and box plots (using the

median) were extrapolated. Categorical data of more than one variable was analysed with cross-tabulation, and the Pearson & M-L Chi square test applied.

Results

60 shortlisted subjects' files were available at CHBAH records. The median age was 13 years and the mean age of presentation was 15 years, 95% CI (12.05, 17.99) (Fig.1). 70% of the patients were males. 16,7% (n = 10) were immunocompromised (4 had HIV, 3 were malnourished, 1 had tuberculosis, 1 was diabetic, and 1 suffered from a combination of alcohol abuse and malnutrition). The median age of presentation of the immunocompromised subset was 19 years. Only 5 (50%) of the 10 immunocompromised patients had a history of sinusitis (Fig. 2). However, 64% (n=32) of the immunocompetent patients had empyema subsequent to sinusitis (p = 0.913), while 8% (n = 4) had a history of head trauma/cranial surgery/dental extraction and had preceding meningitis respectively (Fig. 3).

Table 1. CHBAH SDE Patients

Characteristics	Findings
n	60
Age, mean ± SD (years)	15 ± 11.49
Male (%)	70
Immunocompromised (%)	16.7
Intercurrent sinusitis (%)	61.7
Preceded by meningitis (%)	11.7
Presentation with seizures (%)	40
Presentation with headaches (%)	35
Eye involvement (%)	33.3
Hemiparesis (%)	33.3
Median GCS (/15)	13
Initial white cell count, mean ± SD (x 10^3/µl)	16.63 ± 7.318
C-reactive ptotein, mean ± SD (mg/dl)	153 ± 126
Microorganism 3rd generation cephalosporin sensitivity rate (%)	78.6
Duration of admission, mean ± SD (days)	25.98 ± 19.56
Residual neurological deficit rate (%)	33.3
Mortality rate (%)	13.3

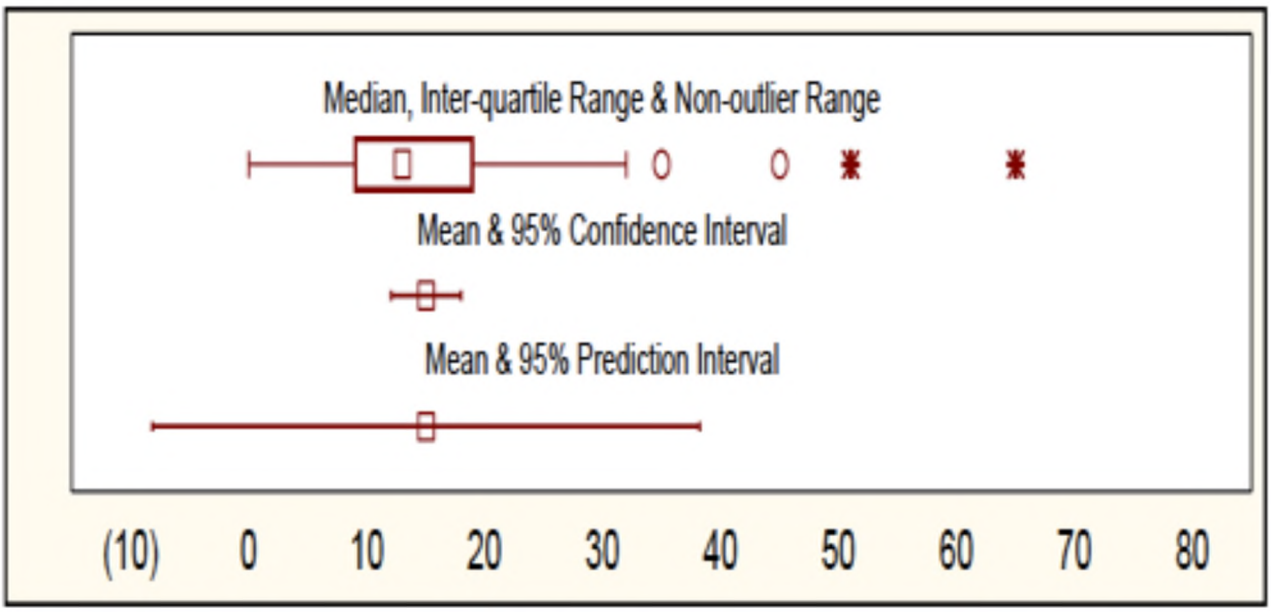

Fig. 1 Box plot of study population's age

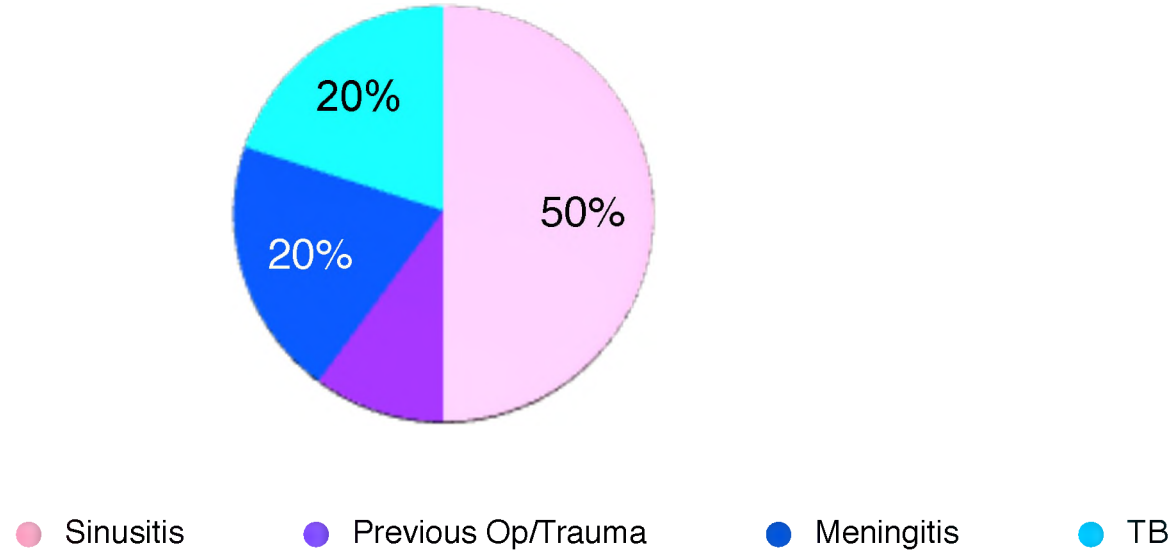

Fig. 2 Pie chart: SDE aetiology in immunocompromised patients

Overall, 11.86% arrived with a Glasgow Coma Score of 8 or less. The median GCS was 13/15. 35% gave a clear history of headaches. 40% were brought in with seizures. 33.3% reached the hospital with a hemi-/mono-paresis/-plegia. 25% presented with eye involvement, and 10% were aphasic.

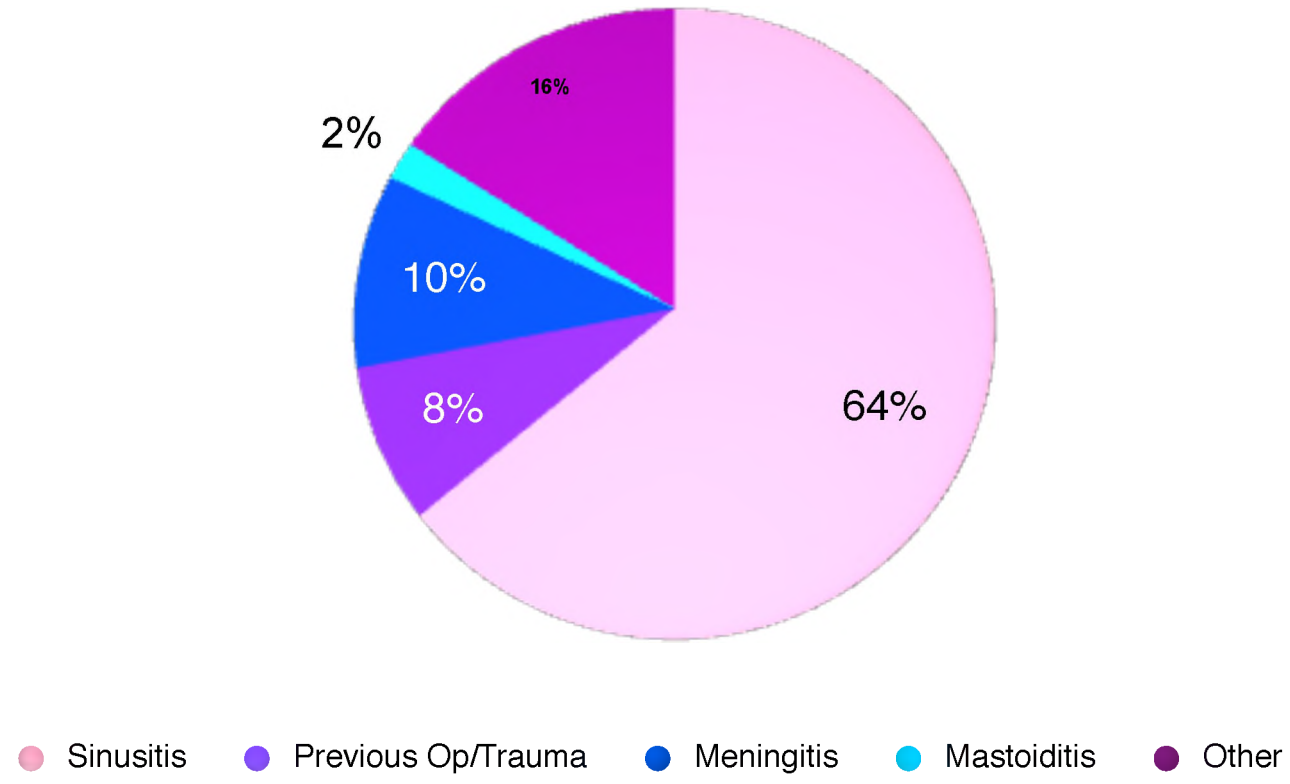

Fig. 3 Pie chart: SDE aetiolgy in immunocompetent patients

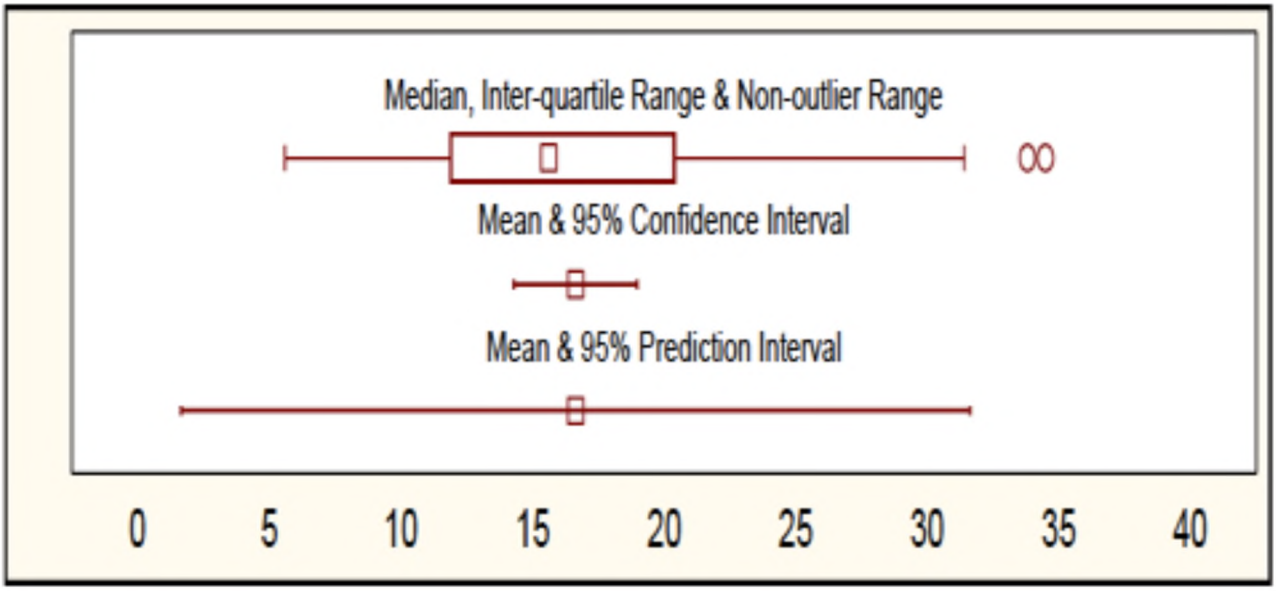

Fig. 4 Box plot of admission white cell count of SDE patient

The mean white cell count was 16.63 x 10^3/μL (95% CI (14.29, 18.97)) (Fig. 4), and mean C-reactive protein was 152.59mg/dL (95% CI (104.47, 200.70)) (Fig. 5). Microorganisms were successfully cultured in 14 patients (23.3%). Among them, 57.1% (n = 8) were infected with

Streptococcus spp. with the following distribution: 37.5% ß-haemolytic *Streptococcus pyogenes,* 25% had *Streptococcus milleri (*viridans group), 12.5% had *Streptococcus angionosus* and 25% unspecified *Streptococcus spp*. One of the patients had a mixed growth, incl. *Streptococcus milleri,* a penicillin resistant, oxacillin sensitive *Staphylococcus aureus*, and the gram negatives *Prevotella spp.* and *Citronella koseri*. The rest of subset consisted of 7.1% each of methicillin resistant *Staphylococcus aureus* (MRSA), the anaerobic gram-positive *Peptostreptococcus,* and the gram-negatives *Klebsilla* spp., *Proteus mirabilis* and *Escherichia coli* (Fig. 6). The cases with gram negative bacterial isolates were those with a history of operative procedures or with immunocompromise (Fig. 7).

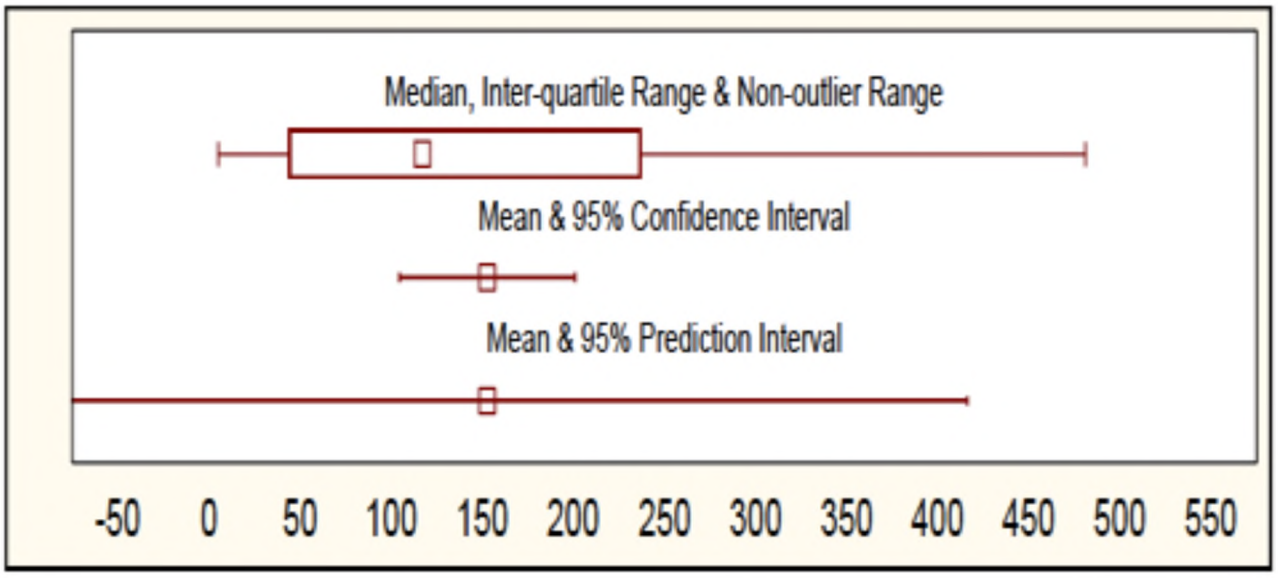

Fig. 5 Box plot of the SDE patients' admission C-reactive protein

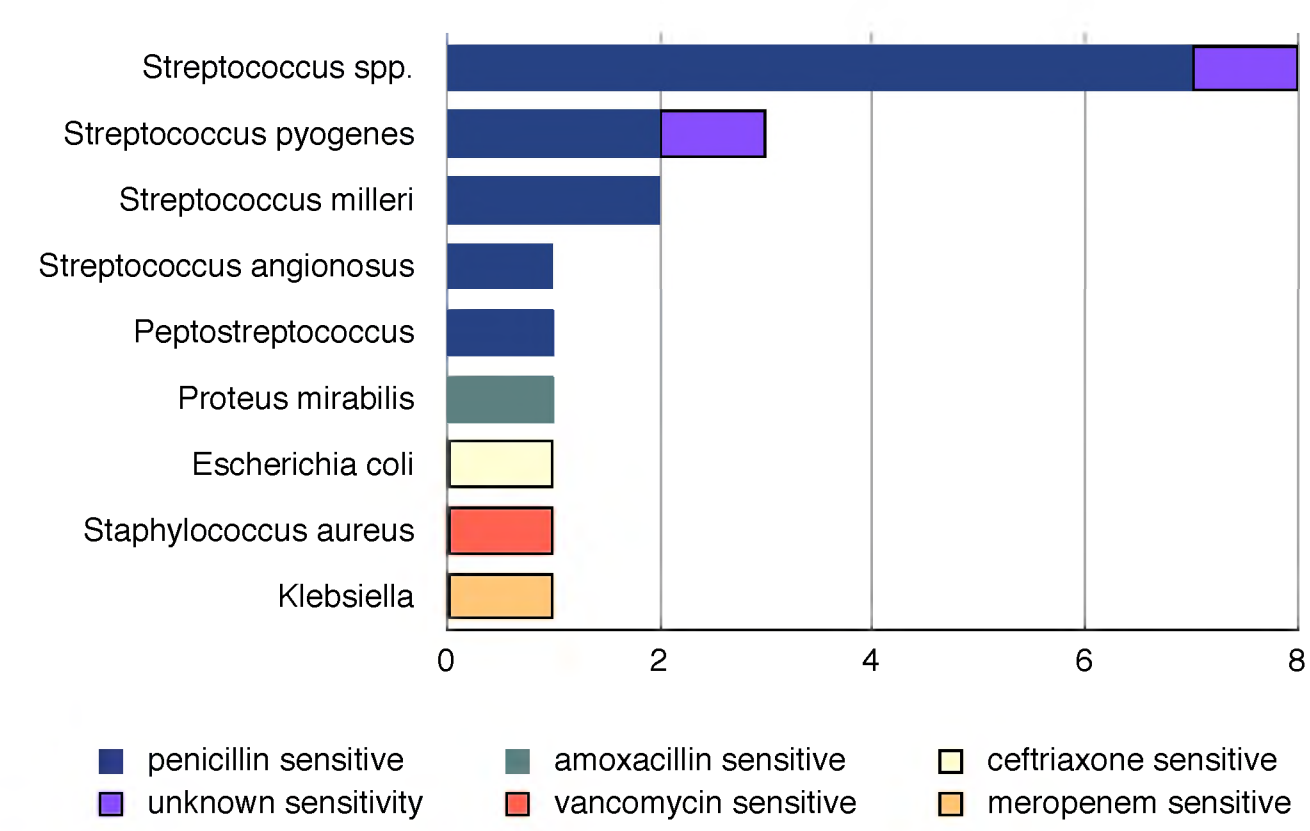

Fig. 6 Histogram of microorganism isolates (non-mixed cases)

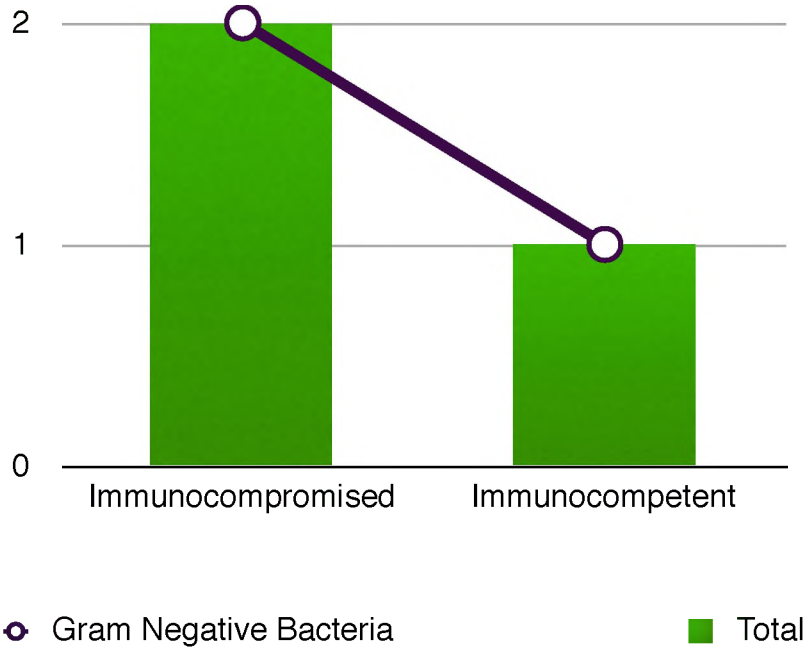

Fig. 7 Histogram of the association between gram negative bacteria isolates and post-operative SDE cases

78.6% (n=11) of the micro-organisms were sensitive to 3rd generation cephalosporins. The sensitivity of one of the *Streptococcus pyogenes* was unknown. In 14.3% (n = 2) of the culture positive population, the microorganisms showed significant resistance, ie. MRSA and *Klebsiella* (an extended spectrum beta-lactamase producer). Both cases were immunocompromised patients - 50% of the four immunocompromised patients whose micro-organisms were identified. However, we could not infer statistical mortality relevance, as the MRSA patient died, but the patient with the *Klebsiella* survived, despite having received the 3rd generation cephalosporin, cefotaxime, as empiric treatment.

13.3% (n = 8) of the patients died (Fig. 8). There was a distinct correlation between mortality and the presence of immunocompromise (Fig. 8). 50% (n = 4) of the patients who perished were immunocompromised. Therefore, 40% of the 10 immunocompromised patients died. This meant that the mortality rate of the immunocompetent patients (8.7%), was in keeping with an absolute risk reduction of 31.3%. One of only three patient treated by means of first-line craniotomy died (Fig. 9). There was no correlation between the mortality and the presenting GCS, focal neurological deficit, haemodynamic stability or eye involvement in our study population.

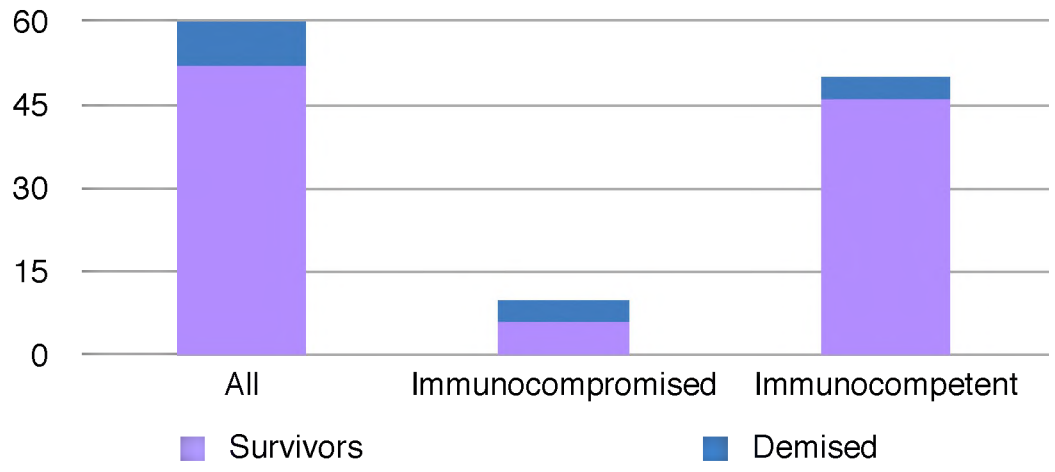

Fig. 8 Histogram of the mortality rate according to immune status

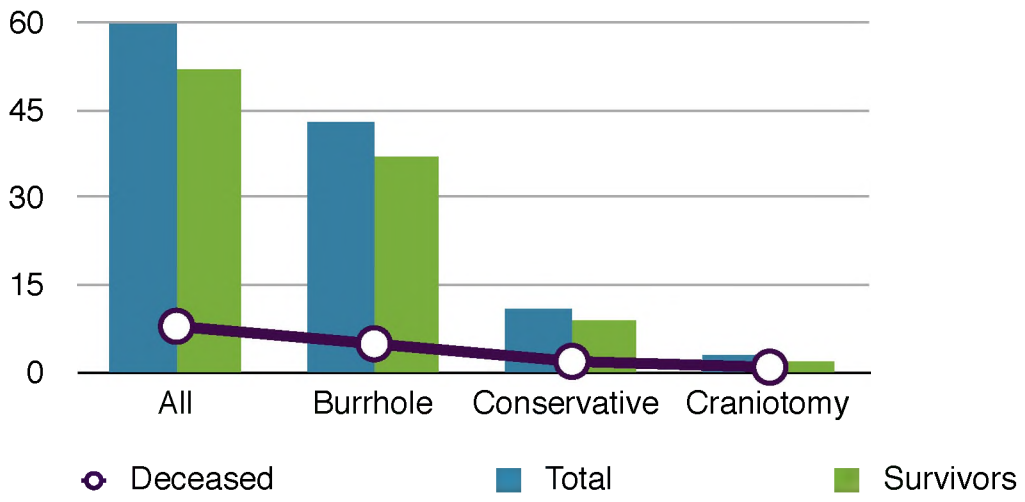

Fig. 9 Histogram of the mortality according to management

Discussion

Our patient's gender distribution approached that of the research population of the New Jersey group (males made up 83.3% of a total of 12 patient). [1] However, our patients' presentation findings differed from theirs, but resembled those of a much older study (by Kaufman et al), which ran in 1974 - before the computer tomography era.[2] However, the latter's patients had a greater burden of otitis and meningitis.[2]

Singh and colleagues investigated 127 sinogenic subdural empyema patients closer to home - in KwaZulu Natal (KZN). Their patients' clinical presentations were more similar to those of the international groups than to ours, as the common clinical findings were fever (68%), headache (54% compared to our study's 35%), orbital inflammation (41.5%, compared to our study's 33.3%). Our figures were closer to each other regarding the prevalence of hemiparesis (their population's 35% versus our 33.3%). Their mortality rate was a mere 11%, similar to ours. The KZN article excluded patients with non-sinogenic aetiology (possible bias, as we found that the patients who

were immunocompromised were more likely to have another causes of SDE, and were at a greater risk of death).[3]

What we agreed on, was that SDE caused a significant case load in South Africa.[3] The KZN and Brisbane researchers spoke in accord on the cause of death: delayed surgical intervention.[3,4] The Australian retrospective study patients (total of 18, 8 of whom had SDE due to paranasal sinusitis) blamed misdiagnosis (and resultant delayed surgical management) due to false negative non-contrast CT scan findings too.[4]

Despite the number of deaths seen in all the studies, Agrawal and his colleagues in Leeds were of the opinion that there was an improvement in outcome relative to the 100% mortality rate of the pre-antibiotic era.[5] The review ruled that the developing world still had a 100% mortality, and that the first world had a 6-35% mortality.[5] The South African studies, Natal and ours, had mortality figures more in keeping with so-called first world outcomes.[3] Furthermore, they related the gains in prognosis to early, appropriate antibiotics and surgery, the pre-operative state, and compliance with anti-epileptic therapy.[5] We, like them, saw a male predominance (they had 80% male patients), but meningitis was more frequent in our adults with HIV and was spread throughout the age groups, rather than being limited to infants in the Leeds study.[5] The micro-organisms most often cultured were *Streptococcus milleri,* and in the post-operative sepsis cases, gram negative bacilli.[5] Their recommendation for empiric antibiotics was a combination of vancomycin, a 3rd generation cephalosporin and metronidazole. They did not propose an alternative for the empiric treatment of SDE in post-operative/immunocompromised patients.[5]

Bockova and Rigamonti of Johns Hopkins University, Baltimore, performed a review of the literature on the topic.[6] They reiterated Agrawal's statement that the beginning of the antibiotic era

was a major turning point in the management of subdural empyema (from almost 100% mortality to over 90% survival).[5,6] Furthermore, the Johns Hopkins group maintained that *Haemophilus influenza* vaccination not only prevented bacterial meningitis (and therefore SDE) and also affected a unimodal peak shift from infancy, to teenage and young adulthood.[6] Their results reflected that 70% of the SDE cases were the result of paranasal sinusitis complications, 10-20% due to otitis media, the rest were associated with post-trauma/-surgery sepsis, or meningitis.[6] Bockova and Rigamonti's article differed from that of Agrawal. The former proposed that *Streptococcus milleri* (esp. *Streptococcus intermedius*) was responsible in only 44-61% - Agrawal stated 81%.[5,6] Even though Agrawal et al's findings were not limited to the paediatric population, the Johns Hopkins review was about children specifically.[5,6] The Baltimore pair further divided the condition into acute (often due to contiguous spread of infection), subacute (usually the result of post-operative/-traumatic infection, and resultant thrombophlebitis & infarction) and subdural empyema of infancy (generally the consequence of meningitis).[6]

The Johns Hopkins group specified the surgical treatment of choice (burrholes in critically ill patients and craniotomies in more resilient candidates) based on a 20% mortality rate in the burrhole population, and 17 % mortality in the patients who had craniotomies performed, as cited from a 1997 textbook by Sagher and their own experience (potential bias: the sicker patient were selected to have burrholes done, hence it slanted the results in favour of craniotomies).[6] 33.3% (n = 1) of the three patients we drained by means of a craniotomy as a first-line operation died. Our study's numbers were insufficient for statistical significance. Bockova and Rigamonti stressed that delayed appropriate medical and surgical treatment, the severity of the neurological deficit and a young age were poor prognostic factors.[6] Although the survival rate soared since 1944 (because of wide-spread administration of penicillin in the management of subdural empyema), the risk of

permanent neurological sequelae (incl. seizures) was up to 44% - ours was 33.3% at the time of discharge from hospital.[6]

Meningitis in the infant population was the most frequent source in the least reproducible of all the retrospective cohorts, by Wu et al from Taiwan.[7] (It was a study done prior to the 1st of March 2010, when the Taiwan added *Haemophilus influenza* B vaccination to the national schedule for infants, see http://tcgwww.taipei.gov.tw/ct.asp?xItem=1124251&ctNode=9923&mp=109012.) 87.1% of the 31 patients studied were infants, and only 9.7% had a history of an otorhinolaryngeal infection.[7] The most common pathogen was *Streptococcus pneumoniae* (not *milleri* or *pyogenes)*. The overt presenting signs were pyrexia (96.8%), seizures (70.1%) and neurological deficit (58.1%).[7]

Beckham and Tyler submitted a review which explored the importance of *Haemophilus influenza B* and *Streptococcus pneumoniae* vaccines in the reduction of infant intracranial sepsis.[8] The article mentioned cranial SDE in only one of twelve pages making up the body of the study. Statistics were only mentioned in reference to the rate of *Staphylococcus aureus* in post-surgical SDE (46%).[8] What Beckham and Tyler forfeited in specificity they gained in validity (the broad statements were substantiated in the other literature we discussed).[7,8,10,11,12]

All the reviews, bar the one by Beckham and Tyler, stated that the special investigation of choice was post-gadolinium MRI.[5,6,9,10,11] Empiric antibiotics of choice were vancomycin and 3rd generation cephalosporins (and metronidazole in post-operative/trauma cases).[5,6,9,10,11] Parenteral antibiotics for 2-3 weeks should form part of a total 6 week therapeutic regimen.[5,6,9,10,11]

The Lancet case report by Osborn and Steinberg raised the importance of recognising orbital complications, as they co-existed with intracranial infection in up to 45% of cases (as opposed to

33.33% of our patients).[10] Their acute sinusitis data showed the presence of Streptococcus milleri and anaerobes, but not the rest of the microorganisms (eg. *Streptococcus pneumoniae*, *Haemophilus influenza*) mentioned by the other researchers in this discussion. [5,6,7,9,10,11] Osborn and Steinberg delved into the pathophysiology of the spread of sepsis from the sinuses (particularly the frontal sinuses).[10] They attributed it to either direct extension (through dura and bone, i.e. osteomyelitis) and/or retrograde thrombophlebitis via the valveless diploic veins into the intracranial venous sinus system.[7,10] The young male predisposition (3-8:1 male-to-female ratio) was phrased as the result of both increased diploic vascularity (esp. in the healthy individuals), as well as the development of frontal sinuses at this age (2nd and 3rd decades of life).[10] In infants, the infection of subdural effusions was usually secondary to meningitis.[10] They related the presenting neurological deficits to oedema (due to post-thrombophlebitic venous stasis with/without infarction).[10]

The Lancet study classified SDE as an acute condition.[10] Brain abscess and epidural empyema patients were thought to have a more indolent course.[10] Seizures were found in 8-20% of SDE patients in the publications interrogated, but in 40% of CHBAH cases. While the other studies delineated post-antibiotic era mortality improvement, the Lancet authors saw a change in the post-CT (2-7% versus 77 % pre-CT) era mortality rate too.[5,10] However, Osborn and Steinberg's stance was that post-contrast MRI was the current diagnostic gold standard (however, they acknowledged the recent technological advances in CT scan quality). Their mortality and morbidity figures approached those of the other reviews.[7,9,10,11] The management recommendation was the same as other meta-analyses: early treatment as it prevented residual neurological deficits in nearly half of the patients.[7,9,10]

De Bonis et al's meta-analysis was the only one to conclude that the SDE source in developed countries was post-surgical/-traumatic sepsis, and that in developing countries the source was

otorhinogenic infection.[11] The microorganisms seen in the other studies, were also present in the Italian paper.[11] Their finding regarding timing echoed that of the Lancet study: presentation was usually acute.[10,11] De Bonis and colleagues were the only team to add "idiopathic" to their pathogenesis list.[11] De Bonis stipulated the terms for conservative treatment (mentioned in passing by Agrawal et al, the only other group to justify this therapeutic option) - (1) a stable patient without neurological fallout; (2) a small loculated collection and (3) improvement with antibiotics.[5,11] They disputed Johns Hopkins's support of craniotomy over burrholes, because reliable literature stipulating appropriate surgical technique "does not exist", although they admitted that there are studies which show a higher mortality in the burrholes group.[6,11] None of the studies used in their review (incl. the Bockanova and Rigamonti article) were randomized controlled trials.[6,11]

Nickerson and colleagues' article was a review of the role of neuroimaging in intracranial infections.[12] The MRI armamentarium was explored in the diagnosis of empyema. Not only was post-gadolinium MRI of significance, but also the improvement in specificity and sensitivity (compared to CT scan, which is the study we have the greater access to) was boosted by characteristic pus restriction (hyperintensity) on diffusion-weighted images, and low (hypointense) apparent diffusion coefficient (ADC) values.[12] MR spectroscopy was employed in the differentiation of pus from other cystic pathology.[12] The review's team of radiologists correlated the imaging with clinical scenarios - but did not dwell on therapy (outside the scope of the article, but relevant to the purposes of our research).[12]

Conclusion

Subdural empyema carried a 13.3% mortality. Although SDE risk factors tended to be complicated sinusitis, immunocompetence, male gender and youth, our null hypothesis (subdural empyema is frequently a complication of sinusitis) was refuted. Vaccination programmes and ear care alleviated the SDE burden caused by complicated meningitis (esp. in infants) and otitis. Older, immunocompromised SDE patients had the highest risk of death. Post-operative cases were all afflicted with gram negative bacterial infections. Resistant organisms, though few, were present only in the immunocompromised subgroup. More subjects and preferably a randomised control trial would help to establish if the administration of empiric vancomycin/carbapenem in immunocompromised patients could improve the outcomes in this subset. Although post-contrast CT scan was credited with important improvements in patient management (and subsequent outcomes), we usually fell short of the international diagnostic gold standard which was post-gadolinium MRI. Our study's mortality and residual deficit rates were comparable to international standards, but the incidence of SDE (and SDE due to meningitis) was still relatively high. Other studies showed the potential dividends of shortening our delays prior to patient admission and to the commencement of therapy, of maintaining a high an index of suspicion when managing sinusitis, and of long-term follow-up.

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